elf atochem

ATO

Elf Atochem North America, Inc.
2000 Market Street
Philadelphia, PA 19103-3222
Tel.: 215.419.7000

8EHQ - 1198 - 14315

MR 12462

November 16, 1998

UPS NEXT DAY DELIVERY

8EHQ-98-14315

Contains No CBI

Document Control Office (7407)
Office of Pollution Prevention and Toxics
U.S. Environmental Protection Agency
401 M Street, S.W.
Washington, DC 20460
Attn: 8(e) Submission

RECEIVED
OPPT CBIC
98 NOV 18 PM 12:

Dear Sir/Madam:

Elf Atochem North America, Inc. (Elf Atochem) is submitting results of a primary skin irritation study in rabbits to the Environmental Protection Agency (EPA) pursuant to the Toxic Substances Control Act (TSCA) Section 8(e). This study provides information on t-amyl hydroperoxide (CAS No. 3425-61-4). It does not involve effects in humans.

Nothing in this letter or the enclosed study is considered confidential business information of Elf Atochem.

The results of this study showed the test material to be corrosive to the skin of rabbits after a 4-hour exposure.

Further questions regarding this submission may be directed to me at (215) 419-5890.

Best Regards,

Debra Randall, DABT
Product Safety Manager

88990000034

RECEIVED
OPPT NCIC
98 DEC -1 PM 12: 38

CONFIDENTIAL

SPONSOR
Elf Atochem S.A.
(in association with Akzo-Nobel and Peroxid-Chemie)
Cours Michelet
La Défense 10
92091 Paris-la-Défense CEDEX
France

TEST SUBSTANCE
LUPEROX TAH 85

STUDY TITLE
ACUTE DERMAL IRRITATION IN RABBITS

STUDY DIRECTOR
Xavier Manciaux

STUDY COMPLETION DATE
25 August 1998

PERFORMING LABORATORY
CIT
Centre International de Toxicologie
Miserey - 27005 Evreux - France

LABORATORY STUDY NUMBER
16566 TAL

CONTENTS

STATEMENT OF THE STUDY DIRECTOR

The study was performed in compliance with the principles of Good Laboratory Practice as described in:

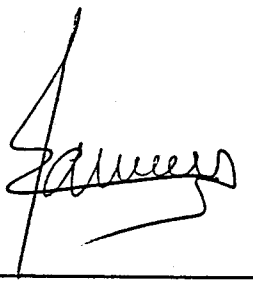
. OECD principles of Good Laboratory Practice, Decision Concerning Mutual Acceptance of Data in the Assessment of Chemicals, C(81)30(final) Annex 2. May 12, 1981 (and amendment).

. Décret N° 90-206 du 7 mars 1990 concernant les Bonnes Pratiques de Laboratoire (Journal Officiel du 9 mars 1990), Ministère de l'Industrie et de l'Aménagement du Territoire.

. Council Directive 87/18/EEC of 18 December 1986 on the harmonization of laws, regulations or administrative provisions relating to the application of the Principles of Good Laboratory Practice and the verification of their applications for tests on chemical substances (OJ No. L 15 of 17.1.87).

I declare that this report constitutes a true and faithful record of the procedures undertaken and the results obtained during the performance of the study.

This study was performed at CIT, Centre International de Toxicologie, Miserey, 27005 Evreux, France.



Toxicology

X. Manciaux Date: 25 August 1998
Study Director
Doctor of Pharmacy

OTHER SCIENTISTS INVOLVED IN THIS STUDY

For Pharmacy: P.O. Guillaumat
Doctor of Pharmacy

For Toxicology: C. Pelcot
Study Supervisor

STATEMENT OF QUALITY ASSURANCE UNIT

Type of inspections	Dates		
	Inspections	Reported to Study Director (*)	Reported to Management (*)
Protocol	11 May 1998	10 July 1998	10 July 1998
Report	10 August 1998	19 August 1998	19 August 1998

At about the same time as the study described in this report, "process-based" and routine facility inspections of critical procedures relevant to this study type were made by the Quality Assurance Unit.
The findings of these inspections were reported to the Study Director and to CIT Management.

The inspections were performed in compliance with CIT Quality Assurance Unit procedures and the Good Laboratory Practice.

The reported methods and procedures were found to describe those used and the results to constitute an accurate and complete reflection of the study raw data.

L. Valette-Talbi Date: 25 August 1998
Doctor of Biochemistry
Head of Quality Assurance Unit
and Scientific Archives

(*) The dates indicated correspond to the dates of signature of audit reports by Study Director and Management.

SUMMARY

At the request of Elf Atochem S.A., Paris-la-Défense, France, the potential of the test substance LUPEROX TAH 85 (batch No. 906-9802-133) to induce skin irritation was evaluated in rabbits according to OECD (No. 404, 17th July 1992) and EC (92/69/EEC, B.4, 31st July 1992) guidelines.
The study was conducted in compliance with the principles of Good Laboratory Practice Regulations.

Methods

The study design was established according to available information on the test substance and the above guidelines.

The test substance was applied in a first assay for periods of 3 minutes and 4 hours to one male New Zealand White rabbit.

As the test substance showed corrosive properties in the first assay, the study was considered complete and the test substance was not evaluated on other animals.

A single dose of 0.5 ml of the undiluted test substance was applied to the closely-clipped skin of each flank. The test substance was held in contact with the skin by means of a semi-occlusive dressing.

Cutaneous reactions were observed approximately 1 hour, 24, 48 and 72 hours after removal of the dressing and then daily until day 9.

The mean values of the scores for erythema and oedema were calculated.

Results

After a 3-minute exposure:
A well-defined or moderate erythema was observed between day 1 and day 5 and a slight oedema was noted between day 1 and day 4. A thickening and a black colouration of the skin were noted from day 5.

After a 4-hour exposure:
A severe erythema and a slight or severe oedema were observed from day 1. Signs of necrosis were observed from day 2; they have masked the evaluation of cutaneous reactions from day 5. A tissular destruction was recorded on day 9.

The animal was killed on day 9 for ethical reasons.

Conclusion

Under our experimental conditions, the test substance LUPEROX TAH 85 (batch No. 906-9802-133) is corrosive when applied topically to rabbits for 4 hours.

RESUME

A la demande de Elf Atochem S.A., Paris-la-Défense, France, les propriétés irritantes du produit LUPEROX TAH 85 (lot n° 906-9802-133) après application cutanée ont été évaluées chez le Lapin selon les lignes directrices de l'OCDE (n° 404, 17 juillet 1992) et de la CEE (92/69/EEC, B.4, 31 juillet 1992).
L'étude a été réalisée conformément aux règles de Bonnes Pratiques de Laboratoire.

Méthode

L'étude a été réalisée selon les informations disponibles sur le produit et les lignes directrices mentionnées ci-dessus.

Lors d'un premier essai, le produit a été appliqué pendant 3 minutes et 4 heures sur 1 lapin mâle New Zealand White.

Le produit ayant montré des propriétés corrosives lors de ce premier essai, aucun autre animal n'a été traité et l'étude a été considérée comme terminée.

Une dose unique de 0,5 ml de produit non dilué a été appliquée sur une surface de peau tondue d'un des flancs. Le produit a été maintenu en contact avec la peau au moyen d'un pansement semi-occlusif.

Les réactions cutanées ont été observées environ 1 heure, 24, 48 et 72 heures après l'enlèvement du pansement puis quotidiennement jusqu'au jour 9.

La moyenne des scores a été calculée pour l'érythème et pour l'oedème.

Résultats

Après une exposition de 3 minutes :
Un érythème bien défini ou modéré est observé entre les jours 1 et 5 et un léger oedème est noté entre les jours 1 et 4. Un épaississement et une coloration noire de la peau sont notés à partir du jour 5.

Après une exposition de 4 heures :
Un érythème sévère et un oedème léger ou sévère sont observés à partir du jour 1. Des signes de nécrose sont notés à partir du jour 2 ; ils masquent l'évaluation des réactions cutanées à partir du jour 5. Une destruction tissulaire est enregistrée au jour 9.

L'animal est sacrifié au jour 9 pour des raisons éthiques.

Conclusion

Dans nos conditions expérimentales, le produit LUPEROX TAH 85 (lot n° 906-9802-133) est considéré corrosif lorsqu'il est appliqué sur la peau chez le lapin pendant 4 heures.

1. INTRODUCTION

The objective of this study was to evaluate the potential of the test substance LUPEROX TAH 85 to induce skin irritation following a single topical application to rabbits.

In the assessment of the toxic characteristics of a test substance, determination of the irritant and/or corrosive effects on the skin of mammals is an important initial step. Information derived from this test serves to indicate the possible hazards likely to arise from exposure of the skin to the test substance.

This study was conducted in compliance with:
. OECD guideline No. 404, 17th July 1992.
. EC Directive No. 92/69/EEC, B.4, 31st July 1992.

2. MATERIALS AND METHODS

2.1 TEST SUBSTANCE

2.1.1 Identification

The test substance LUPEROX TAH 85 used in the study was supplied by Elf Atochem S.A.

The test substance was identified as follows:
. name:
  - protocol and labelling: HYDROPEROXYDE DE-t-AMYLE/ LUPEROX TAH 85
. batch number:
  - protocol and labelling: 906-9802-133
. Elf Atochem filing number: CAL 1159/98
. description: colourless liquid
. container: one plastic flask
. date of receipt: 7 April 1998
. storage conditions: at room temperature and protected from light
. expiry date: September 1998.

Data relating to the characterization of the test substance are documented in a test article description and an analytical certificate (presented in appendix 1) provided by the Sponsor.

The pH of the test substance, measured at CIT, was approximately 3.

2.1.2 Formulation procedure

The test substance was used undiluted.

2.2 TEST SYSTEM

2.2.1 Animal

Sex, species, strain: male New Zealand White rabbit.
Justification of the test system : species generally accepted by regulatory authorities for this type of study.
Breeder: Elevage Cunicole de Val de Selle, 80160 Prouzel, France.
Number and identification: one animal was used. The animal was identified with a metal tag in the ear.
Weight: on the day of treatment, the animal had a body weight of 2.4 kg.
Acclimatization: at least 5 days before the beginning of the study.

2.2.2 Environmental conditions

The conditions in the animal room were set as follows:
. temperature: 18 ± 3°C
. relative humidity: 30 to 70%
. light/dark cycle: 12 h/12 h
. ventilation: approximately 12 cycles/hour of filtered, non-recycled air.
The temperature and relative humidity were under continuous control and recording. The records were checked daily and archived. In addition to these daily checks, the housing conditions and corresponding instrumentation and equipment were verified and calibrated at regular intervals.
The animal was housed in a polystyrene cage (35 cm x 55 cm x 32 cm or 48.2 cm x 58 cm x 36.5 cm) equipped with a food container and a water bottle.

2.2.3 Food and water

During the study, the animal had free access to 112 C pelleted diet (UAR, 91360 Villemoisson-sur-Orge, France).
Each batch of food was analysed by the supplier for composition and contaminant levels.
The diet formula is presented in appendix 2.

Drinking water filtered by a FG Millipore membrane (0.22 micron) was provided *ad libitum*.
Bacteriological and chemical analysis of the water and diet, including the detection of possible contaminants (pesticides, heavy metals and nitrosamines), are performed regularly by external laboratories.
The results of these analyses are archived at CIT.

No contaminants are known to be present in the diet or drinking water at levels which may be expected to interfere with or prejudice the outcome of the study.

2.3 TREATMENT

2.3.1 Preparation of the animal

The day before treatment, both flanks of the animal were clipped using electric clippers and its skin was examined in order to ensure that the animal had healthy intact skin at the beginning of the study.

2.3.2 Study design

The study design was established according to available information on the test substance and the OECD (No. 404) and EC (92/69/EEC, B.4) guidelines.

As possible irritant effects were anticipated, the test substance was evaluated in one animal (No. 01) in a first assay. The duration of exposure was 3 minutes on one flank and 4 hours on the other flank.

Since the test substance showed corrosive properties in this first assay, the study was considered complete and the test substance was not evaluated on other animals.

2.3.3 Application of the test substance

The test substance was used undiluted.

Doses of 0.5 ml of the test substance were placed on a 6 cm^2 dry gauze pad, which was then applied to the right flank (application for 4 hours) or the left flank (application for 3 minutes) of the animal.

The test substance and the gauze pad were held in contact with the skin by means of an adhesive hypoallergenic aerated semi-occlusive dressing and a restraining bandage.

The untreated skin served as control.

No residual test substance was observed on removal of the dressing.

2.3.4 Date of treatment

Animal number	Date of treatment (day 1)	End of the observation period
01	23 June 1998	1 July 1998
	(application for 3 minutes and 4 hours)	

2.4 CUTANEOUS EXAMINATIONS

The skin was examined approximately 1 hour, 24, 48 and 72 hours after removal of the dressing.

Following the OECD and EC guidelines:
. when there was no evidence of dermal irritation after 72 hours, the study was ended.
. when there was persistent cutaneous irritation after 72 hours, the observation period was extended to a maximum of 14 days (until day 15) in order to determine the progress of the lesions and their reversibility.
. when severe irritant effects were observed, the animals were killed on humane grounds.

Any change in the animals' behaviour was noted.

2.5 DESCRIPTION AND EVALUATION OF CUTANEOUS REACTIONS

Dermal irritation was evaluated for the animal according to the following scoring scale:

Erythema and eschar formation:

. no erythema	0
. very slight erythema (barely perceptible)	1
. well-defined erythema	2
. moderate to severe erythema	3
. severe erythema (beet redness) to slight eschar formation (injuries in depth)	4

Oedema formation

. no oedema	0
. very slight oedema (barely perceptible)	1
. slight oedema (edges of area well-defined by definite raising)	2
. moderate oedema (raised approximately 1 millimetre)	3
. severe oedema (raised more than 1 millimetre and extending beyond area of exposure)	4

Any other lesions were noted.

2.6 INTERPRETATION OF RESULTS

The results obtained were evaluated in conjunction with the nature and the reversibility of the findings observed.

2.6.1 Criteria for irritation

A substance or a preparation is considered to be irritating to the skin if, when it is applied to healthy intact animal skin for up to 4 hours, significant inflammation is caused and which persists for 24 hours or more after the end of the exposure period.

2.6.2 Criteria for corrosion

A substance or a preparation is considered to be corrosive if, when it is applied to healthy intact animal skin, it produces full thickness destruction of skin tissue on at least one animal during the test for skin irritation, or if the result can be predicted, for example: from strongly acid or alkaline reactions.

2.7 PROTOCOL ADHERENCE

The study was performed in accordance with Study Protocol No. 16566 TAL and subsequent amendments, with the following deviation from the agreed Study Protocol:
- the temperature recorded in the animal room was sometimes outside of the target ranges specified in the protocol.

This minor deviation was not considered to compromise the validity or integrity of the study.

2.8 ARCHIVING

The study documentation and specimens generated during the course of the study are archived at CIT, 27005 Miserey, Evreux, France, for 10 years after the end of the *in vivo* phase of the study.

The archived study materials include:
. protocol and possible amendments,
. raw data,
. correspondence,
. final report and possible amendments.

On completion of this period, the archived study materials will be returned to the Sponsor, or may be archived at CIT for a further period.

3. RESULTS (tables 1 and 2)

After a 3-minute exposure:
A well-defined or moderate erythema (grade 2 or 3) was observed between day 1 and day 5 and a slight oedema (grade 2) was noted between day 1 and day 4. A thickening and a black colouration of the skin were noted from day 5.

After a 4-hour exposure:
A severe erythema (grade 4) and a slight or severe oedema (grade 2 or 4) were observed from day 1. Signs of necrosis were observed from day 2; they have masked the evaluation of cutaneous reactions from day 5. A tissular destruction was recorded on day 9.

The animal was killed on day 9 for ethical reasons.

4. CONCLUSION

Under our experimental conditions, the test substance LUPEROX TAH 85 (batch No. 906-9802-133) is corrosive when applied topically to rabbits for 4 hours.

Table 1: Individual cutaneous examinations and mean values of the scores recorded at each reading (24, 48 and 72 hours) (exposition for 3 minutes)

Rabbit number	Dermal Irritation	Scores				Mean irritation score (1)	Interpretation (+) (-)
		1h D1	24h D2	48h D3	72h D4		
01	Erythema	2	2	2	3	2.3	(+)
	Oedema	2	2	2	2	2.0	(+)
	Other	*	*	*	*		

(1) mean of scores on days 2, 3 and 4
h = hour
D = day
(+) = irritant according to E.E.C. criteria

Table 1 (continued)

Rabbit number	Dermal Irritation	Scores				
		D5	D6	D7	D8	D9
01	Erythema	2/No	0/No	0/No	0/No	0
	Oedema	LP	LP	LP	LP	LP
	Other	P	P	P	P	P

D = day
No = Black colouration of the skin
P = Thickening of the skin
LP = Scoring masked by thickening of the skin

Table 2: Individual cutaneous examinations and mean values of the scores recorded at each reading (24, 48 and 72 hours) (exposition for 4 hours)

Rabbit number	Dermal Irritation	Scores				Mean irritation score (1)	Interpretation (+) (-)
		1h D1	24h D2	48h D3	72h D4		
01	Erythema	4	4	4	4	4.0	(+)
	Oedema	2	4	4	4	4.0	(+)
	Other	*	N	N	N		

(1) mean of scores on days 2, 3 and 4
-h = hour
D = day
(+) = irritant according to E.E.C. criteria
(-) = non-irritant according to E.E.C. criteria
* = None
N = Necrosis

Table 2 (continued)

Rabbit number	Dermal Irritation	Scores				
		D5	D6	D7	D8	D9
01	Erythema	LN	LN	LN	LN	DT
	Oedema	LN	LN	LN	LN	DT
	Other	N	N	N	N	N

D = day
N = Necrosis
LN = Scoring masked by necrosis
DT = Tissue destruction

APPENDICES

1. Test article description and analytical certificate

TOXICOLOGY DEPARTMENT
CONFIDENTIAL
27 March 1998
DTI no. 662

elf atochem s.a.
La défense 10, cedex 42
92091 Paris-la-Défense, France

TEST ARTICLE DESCRIPTION

HYDROPEROXYDE DE t-AMYLE (LUPEROX TAH 85)

IDENTITY

Test article name	:	HYDROPEROXYDE DE t-AMYLE
Synonym	:	LUPEROX TAH 85
CAS number	:	3425-61-4
EINECS number	:	222-321-7
Peroxid content	:	87.6% (in water)
Origin	:	Elf Atochem Deutschland
Batch	:	906-9802-133
Elf Atochem filing number	:	CAL 1159/98

PHYSICAL AND CHEMICAL PROPERTIES

Appearance	:	liquid
Specific gravity	:	910 kg/m^3
Solubility	:	partially miscible with water, miscible with organic solvents

TOXICOLOGICAL INFORMATIONS AND USE SAFETY

See Material Safety Data Sheet.

STORAGE AND DISPOSAL

Storage	:	in dark and at room temperature
Expiry date and disposal	:	incineration after September 1998

Elf Atochem Deutschland GmbH
Niederlassung Günzburg
Denzinger Straße 7 · D-89312 Günzburg
Postfach 1354 · D-89303 Günzburg
Tel. (08221) 98-0 · Telefax (08221) 98-166 · Telex 531 121

elf atochem
ATO

Elf Atochem Deutschland GmbH · Postfach 1354 · D-89303 Günzburg

Elf Atochem SA
Centre d'application de Levallois
95, Rue Danton

F-92300 Levallois Perret

VK-017-4 PHE 9510

Client 100015I
Günzburg, 10.03.98

Rechnung Nr. vom
Invoice No. of
Facture No. du
Fattura No. A0BWBM010 del

Ihre Bestellung:
Your Order:
Votre Commande:
Vs. Ordine:

Lieferadresse:
Delivery Address:
Adresse de livraison:
Destinazione:

Analysis with goods -
att. Mr. Bourlay

ANALYSENZERTIFIKAT
CERTIFICATE OF ANALYSIS
CERTIFICAT D'ANALYSE
CERTIFICATO D'ANALISI

0,5 kg LUPEROX TAH 85

Chargen Nr. Batch No. Charge No. Lotto No.	Gebindezahl No. of cont. Nombre de fûts No. di fusti	Peroxidgehalt Assay Teneur en Peroxyde Contenuto di Perossido					
		%					
906-9802-133	1	87,6					
production: 19.02.98							

2. Diet formula

Ref: 112
COMPLETE DIET
RABBIT MAINTENANCE DIET
Appearance: 4.5 mm diameter granules
Conditioning: bags of 25 kgs

Daily portion: in accordance with race and body weight, Rabbits 100-150 g, water *ad libitum*.

FORMULA %	
Cereals	43.8
Grain byproducts and legumes	49
Vegetable protein (soya bean meal, yeast)	4.2
Vitamin and mineral mixture	3

AVERAGE ANALYSIS %	
Calorific value (Kcal/kg)	2200
Moisture	10
Proteins	13
Lipids	2.7
Carbohydrates (N.F.E.)	49.3
Fibre	17
Minerals (ash)	8

AMINO ACID VALUES (calculated in mg/kg)	
Arginine	6800
Cystine	2100
Lysine	4600
Methionine	1600
Tryptophan	1400
Glycine	5200

FATTY ACID VALUES (calculated in mg/kg)	
Palmitic acid	6400
Palmitoleic acid	0
Stearic acid	600
Oleic acid	6400
Linoleic acid	12100
Linolenic acid	2400

MINERALS (calculated in mg/kg)

	Nat. val.	CMV val.	Total
P	3500	3500	7000
Ca	4500	4500	9000
K	11600	0	11600
Na	400	1600	2000
Mg	2100	100	2200
Mn	40	40	80
Fe	160	140	300
Cu	12	15	27
Zn	30	45	75
Co	0.1	1.5	1.6
I	0	0	0
Cl	500	3000	3500

VITAMINS (calculated per kg)

	Nat. val.	CMV val.	Total
Vitamin A	2850 IU	6500 IU	9350 IU
Vitamin D3	30 IU	1000 IU	1030 IU
Vitamin B1	4.3 mg	0 mg	4.3 mg
Vitamin B2	3.8 mg	0 mg	3.8 mg
Vitamin B3	16 mg	0 mg	16 mg
Vitamin B6	1 mg	1 mg	2 mg
Vitamin B12	0 mg	0 mg	0 mg
Vitamin E	16 mg	10 mg	26 mg
Vitamin K3	6 mg	1 mg	7 mg
Vitamin PP	55 mg	5 mg	60 mg
Folic acid	0 mg	0 mg	0 mg
Biotin	0 mg	0 mg	0 mg
Choline	850 mg	200 mg	1050 mg
Meso-Inositol	0 mg	0 mg	0 mg

Available under quality "Control Ref.: 112 C"

UAR, 7 rue Galliéni, 91360 Villemoisson - Tel : 01.69.04.03.57 - Fax : 01.69.04.81.97
(Ref. Doc. UAR : 1992)